8/27/05 10/773,414

NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:27:01 ON 27 AUG 2005

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 17:27:12 ON 27 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 26 AUG 2005 HIGHEST RN 861902-61-6
DICTIONARY FILE UPDATES: 26 AUG 2005 HIGHEST RN 861902-61-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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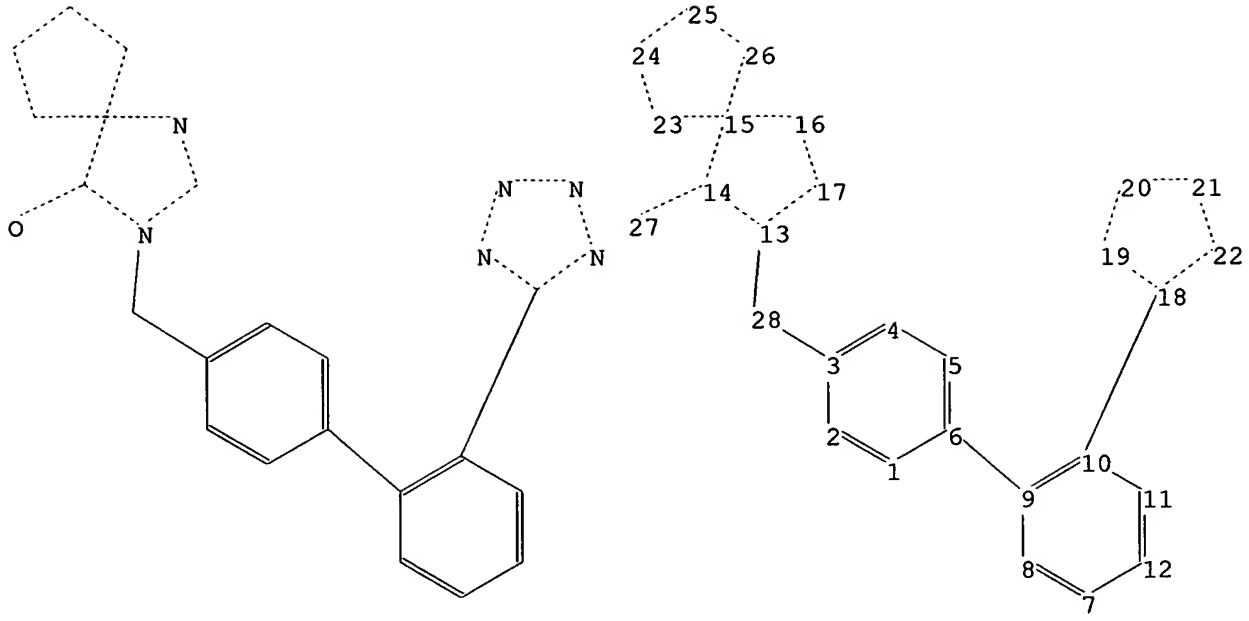
Uploading C:\Program Files\Stnexp\Queries\10773414a.str



chain nodes :
27 28
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
24 25 26
chain bonds :
3-28 6-9 10-18 13-28 14-27
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-17
14-15 15-16 15-23 15-26 16-17 18-19 18-22 19-20 20-21 21-22 23-24 24-25
25-26
exact/norm bonds :
13-14 13-17 13-28 14-15 14-27 15-16 15-23 15-26 16-17 18-19 18-22 19-20
20-21 21-22 23-24 24-25 25-26
exact bonds :
3-28 6-9 10-18
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:CLASS 28:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s L1
SAMPLE SEARCH INITIATED 17:27:35 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 55 TO ITERATE

100.0% PROCESSED 55 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 656 TO 1544
PROJECTED ANSWERS: 2 TO 124

L2 2 SEA SSS SAM L1

=> s L1 full
FULL SEARCH INITIATED 17:27:41 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1139 TO ITERATE

100.0% PROCESSED 1139 ITERATIONS 42 ANSWERS
SEARCH TIME: 00.00.01

L3 42 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 161.33 161.54

FILE 'CAPLUS' ENTERED AT 17:27:44 ON 27 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 27 Aug 2005 VOL 143 ISS 10
FILE LAST UPDATED: 26 Aug 2005 (20050826/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s L3
L4 677 L3

=> s L4 and (synthesi? or "process of making" or "method of making")
1439123 SYNTHESI?

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        2135433 "PROCESS"
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        3177531 "PROCESS"
                  ("PROCESS" OR "PROCESSES")
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            195 "OFS"
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                  ("PROCESS"(W)"OF"(W)"MAKING")
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L5           36 L4 AND (SYNTHESI? OR "PROCESS OF MAKING" OR "METHOD OF MAKING")

=> d ibib abs fhitstr 1-36
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L5 ANSWER 1 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:732585 CAPLUS
DOCUMENT NUMBER: 143:179169
TITLE: Cosmetic compositions ACE inhibitors and/or angiotensin II receptor antagonists for treatment of skin aging
INVENTOR(S): Jensen, Benny Vittrup
PATENT ASSIGNEE(S): Ace Aps, Den.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005072696	A1	20050811	WO 2005-DK65	20050128

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

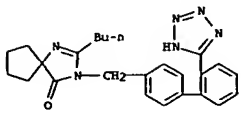
PRIORITY APPLN. INFO.: DK 2004-136 A 20040130
US 2004-553661P P 20040316

AB The present invention relates to a method and cosmetic preparation comprising an ACE inhibitor and/or angiotensin II receptor antagonist present in an amount of about 0.01 to 100 mg/kg each for the treatment of skin aging or wrinkling. For example, an ACE inhibitor, such as lisinopril 10 mg/kg was formulated in a cream base comprising (i) Phase A containing Emulgade SE 4.0%, Cutina MD 1.0%, Lanette O 1.0%, Baysilon M 350 0.5%, Cetiol PGL 7.0%, Cetiol OE 4.0%, and Copherol 1250 0.5%, (ii) Phase B containing D-panthenol 1.0%, glycerin (86%) 5.0%, and water 71.5%, (iii) Phase C containing Carbopol 980 0.2% and Cetiol PGL 1.0%, and (iv) Phase C containing KOH (20%) 0.3% and perfume/preservative as needed.

IT 138402-11-6, Avapro
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Irbesartan; compns. containing ACE inhibitors and/or angiotensin II receptor antagonists for improvement and maintenance of skin tone and treatment of skin aging)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 1 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

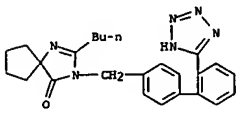
L5 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:640217 CAPLUS
TITLE: Improved synthesis of irbesartan, an antihypertensive active pharmaceutical ingredient
AUTHOR(S): Sumalatha, Bollikonda Satyanarayana Yasareni; Venkatraman, Sundram; Reddy, Ghanta Mahesh; Reddy, Padi Pratap
CORPORATE SOURCE: Research and Development Centre, Dr Reddy's Laboratories Limited, Hyderabad, India
SOURCE: Synthetic Communications (2005), 35(14), 1979-1982
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Taylor & Francis, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An improved synthesis of the antihypertensive drug irbesartan I, based on the Suzuki reaction, was described.

IT INDEXING IN PROGRESS
IT 138402-11-6P, Irbesartan
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of irbesartan antihypertensive active pharmaceutical ingredient based on Suzuki reaction)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:612299 CAPLUS
DOCUMENT NUMBER: 143:133380
TITLE: Preparation of azabicyclic heterocycles as cannabinoid receptor modulators
INVENTOR(S): Gu, Guixue; Ewing, William R.; Mikkilineni, Amarendra B.; Pendri, Annapurna; Ellsworth, Bruce A.; Sher, Philip M.; Gerritz, Samuel; Sun, Chongqing; Murugesan, Natesan; Wu, Ximao
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

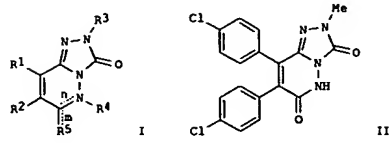
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005063762	A1	20050714	WO 2004-US42878	20041217

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005171110	A1	20050804	US 2004-16198	20041217

PRIORITY APPLN. INFO.: US 2003-531451P P 20031219
US 2004-16198 A 20041217

GI

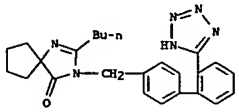


AB The present application describes compds. I [R1, R2 = halo, CN, alkyl, etc.; R3 = H alkyl, alkenyl, cycloalkyl, etc.; R4 is absent when n is a double bond; R4 = H, alkyl, cycloalkyl, etc.; R5 = halo, (un)substituted OH, NH2, etc. when m is a single bond; R5 = O when m = a double bond; m, n = a single or double bond; when m is a single bond, n is a double bond; when m is a double bond, n is a single bond], pharmaceutical compns. comprising at least one compound I and optionally one or more addnl. therapeutic agents and methods of treatment using the compds. I both alone and in combination with one or more addnl. therapeutic agents. Over 40

L5 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
compds. I were prepd. E.g., a multi-step synthesis of II, starting from dichloromandelic anhydride, was given. The exemplified compds. I showed the CB-1 receptor binding Ki values in the range of 0.01 nM to 10000 nM.

IT **138402-11-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of azabicyclic heterocycles as cannabinoid receptor modulators)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:572592 CAPLUS
DOCUMENT NUMBER: 143:97378
TITLE: Preparation of azabicyclic heterocycles as cannabinoid receptor modulators
INVENTOR(S): Yu, Guixue; Ewing, William R.; Mikkilineni, Anarendra B.; Pendri, Annapurna; Sher, Philip M.; Gerritz, Samuel; Ellsworth, Bruce A.; Wu, Gang; Huang, Yanting; Sun, Chongqing; Murugesan, Natesan; Gu, Zhengxiang; Wang, Ying; Sitkoff, Doree; Johnson, Stephen R.; Wu, Ximao
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 196 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20051433381	A1	20050630	US 2004-16135	20041217
WO 2005063761	A1	20050714	WO 2004-US42820	20041217
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2005061509	A1	20050707	WO 2004-US42542	20041220
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PRIORITY APPLN. INFO.: US 2003-531451P P 20031219
US 2004-16135 A 20041217

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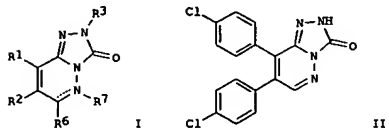


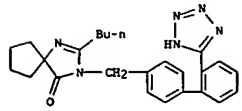
I II

L5 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

AB The present application describes compds. I [R1, R2 = halo, CN, alkyl, etc.; R3 = alkyl, alkenyl, cycloalkyl, etc.; R6 = H, alkyl, cycloalkyl, etc.; R7 is absent when double bond; or R7 = H, alkyl, cycloalkyl, etc.], pharmaceutical compns. comprising at least one compound I and optionally one or more addnl. therapeutic agents and methods of treatment using the compds. I both alone and in combination with one or more addnl. therapeutic agents. Over 400 compds. I were prepared E.g., a multi-step synthesis of II, starting from dibromopyridazinone, was given. Representative compds. I showed the CB-1 receptor binding Ki values in the range of 0.01 nM to 10000 nM.

IT **138402-11-6**, Irbesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; preparation of azabicyclic heterocycles as cannabinoid receptor modulators)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:474941 CAPLUS
DOCUMENT NUMBER: 142:476245
TITLE: Synergistic effect of amlodipine and atorvastatin on aortic endothelial cell nitric oxide release, and therapeutic use
INVENTOR(S): Mason, R. Preston
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U.S. Ser. No. 921,479.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

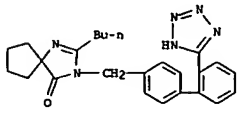
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005119270	A1	20050602	US 2004-987271	20041112
US 2002052394	A1	20020502	US 2001-921479	20010803
US 6835742	B2	20041228		
US 2005009888	A1	20050113	US 2004-911807	20040805

PRIORITY APPLN. INFO.: US 2000-223214P P 20000804
US 2001-921479 A2 20010803

AB The combination of amlodipine and atorvastatin acts to synergistically synthesize NO production Moreover, the addition of a tertiary compound complements this combination of amlodipine and atorvastatin in NO production The combination of the invention may be used to treat arterial and related heart disease.

IT **138402-11-6**, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic effect of amlodipine and atorvastatin on aortic endothelial cell nitric oxide release, and therapeutic use)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:371095 CAPLUS
DOCUMENT NUMBER: 142:423895
TITLE: Methods for controlling mast cell-derived renin and uses in treating conditions with abnormal renin levels
INVENTOR(S): Silver, Randi B.; Levi, Roberto
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005037317	A2	20050428	WO 2004-US33755	20041013

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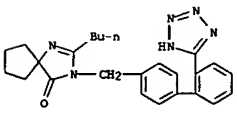
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-512142P P 20031017
AB The invention relates to the discovery that renin is present in mast cells and can act in a localized manner to initiate and/or exacerbate a number of conditions. Thus, the invention provides methods for treating cardiac, vascular, lung, liver, cervical, intestinal, muscle, pancreatic, brain, kidney, skin and other conditions that involve inhibiting the synthesis and/or release of renin from mast cells and/or inhibiting the activity of renin after release from mast cells. The methods of the invention can also involve inhibiting elements of the local renin-angiotensin system (e.g. inhibiting ACE and angiotensin II receptors), thereby inhibiting angiotensin II produced locally from mast-cell-derived renin.
IT 138402-11-6, Irbesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for controlling mast cell-derived renin and uses in treating conditions with abnormal renin levels)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



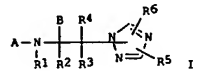
L5 ANSWER 7 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1127349 CAPLUS
DOCUMENT NUMBER: 142:74574
TITLE: Preparation of 1,2,4-triazolylethylamines as modulators of the glucocorticoid receptor
INVENTOR(S): Robinson, Leslie; Rueter, Jaimie K.; Moree, Wilna J.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004111015	A1	20041223	WO 2004-US18487	20040611

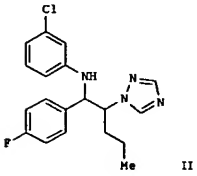
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004266831	A1	20041230	US 2004-865443	20040610

PRIORITY APPLN. INFO.: US 2003-477545P P 20030611
OTHER SOURCE(S): MARPAT 142:74574
GI



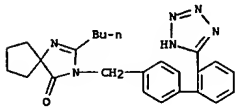
I



II

AB Title compds. I [A, B = cycloalkyl, aryl, heteroaryl; R1 = H, acyl, carboxy, etc.; R2-4 = H, alkyl, heteroalkyl, etc.; R5-6 = H, F, Cl, Br,

L5 ANSWER 7 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
etc.] are prepd. General synthetic procedures are provided for the synthesis of 19 examples, e.g., II. Example compds. are tested in a glucocorticoid receptor binding assay in the range of 0.1 nM to 40 μM [no data]. I are glucocorticoid receptor modulators and are useful in treating diseases requiring glucocorticoid receptor agonist or antagonist therapy such as obesity, diabetes, inflammatory and immune disorders.
IT 138402-11-6, Irbesartan
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; preparation of 1,2,4-triazolylethylamines as modulators of glucocorticoid receptor)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



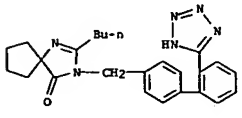
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1124587 CAPLUS
DOCUMENT NUMBER: 142:69188
TITLE: Combination therapy for the treatment of diabetes
INVENTOR(S): Erondu, Ngozi E.; Fong, Tung M.; MacNeil, Douglas J.; Van Der Ploeg, Leonardus H. T.; Kanatani, Akio
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110375	A2	20041223	WO 2004-US17291	20040602
WO 2004110375	A3	20050512		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-476388P P 20030606
OTHER SOURCE(S): MARPAT 142:69188
AB The present invention relates to compns. comprising an anti-obesity agent and an anti-diabetic agent useful for the treatment of diabetes, diabetes associated with obesity and diabetes-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compns., medicaments, and kits useful in carrying out these methods.
IT 138402-11-6, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of diabetes and diabetes-related disorders using antiobesity agent and antidiabetic agent and other agents)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1086422 CAPLUS
DOCUMENT NUMBER: 142:197940
TITLE: Dual Angiotensin II and Endothelin A Receptor Antagonists: Synthesis of 2'-Substituted N-3-Isoxazolyl Biphenylsulfonamides with Improved Potency and Pharmacokinetics
AUTHOR(S): Murugesan, Natesan; Gu, Zhengxiang; Fadnis, Leena; Tellew, John E.; Baska, Rose Ann F.; Yang, Yifan; Beyer, Sophie M.; Monshizadegan, Hossain; Dickinson, Kenneth E.; Valentine, Maria T.; Humphreys, W. Griffith; Lan, Shih-Jung; Ewing, William R.; Carlson, Kenneth E.; Kowala, Mark C.; Zahler, Robert; Macor, John E.
CORPORATE SOURCE: Discovery Chemistry and Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-5400, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(1), 171-179
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

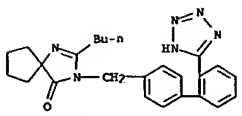
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB In a previous report its was demonstrated that merging together key structural elements present in an AT1 receptor antagonist (irbesartan) with key structural elements in a biphenylsulfonamide ETA receptor antagonist followed by addnl. optimization provided a product which is a dual-action receptor antagonist (DARA), which potently blocked both AT1 and ETA receptors. Described herein are our efforts directed toward improving both the pharmacokinetic profile as well as the AT1 and ETA receptor potency of 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide (I). Efforts centered on modifying the 2'-side chain of I and examining the (isoxazolyl)sulfonamide moiety in I. This effort resulted in the discovery of 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)[1,1'-biphenyl]-2-sulfonamide (II) as a highly potent second-generation DARA. This compound also showed substantially improved pharmacokinetic properties compared to I. In rats, DARA II reduced blood pressure elevations caused by i.v. infusion of Ang II or big ET-1 to a greater extent and with longer duration than DARA I or AT1 or ETA receptor antagonists alone. II clearly demonstrated superiority over irbesartan (an AT1 receptor antagonist) in the normal SHR model of hypertension in a dose-dependent manner, demonstrating the synergy of AT1 and ETA receptor blockade in a single mol. The crystal and mol. structures of II were reported.

IT 138402-11-6, Irbesartan
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation of irbesartan-BMS 193884 combination drug and study of its activity as dual angiotensin II and endothelin A receptor antagonist and its pharmacokinetics)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



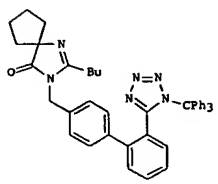
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:696369 CAPLUS
DOCUMENT NUMBER: 141:225515
TITLE: Synthesis of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-zion
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072064	A1	20040826	WO 2004-US3604	20040205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004242894	A1	20041202	US 2004-773414	20040205
PRIORITY APPLN. INFO.:			US 2003-445218P	P 20030205
			US 2003-465905P	P 20030428

OTHER SOURCE(S): CASREACT 141:225515
GI



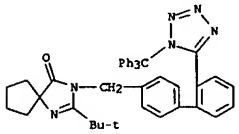
I

AB Provided are 5 methods of making 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-ene-4-one (I), e.g. comprising the steps of: (a) reacting 1-(N'-pentanoylamino)cyclopentanecarboxylic acid amide with 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole in the presence of an inorg. base, a solvent and a phase transfer catalyst; (b) cooling the mixt.; (c) adding water to the mixt. whereby two phases are obtained; (d) sepg. the two phases obtained; and (e) recovering the compd. I. The compds. I can be converted to irbesartan which is a known angiotensin II receptor antagonist (blocker).

L5 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

IT 745814-09-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

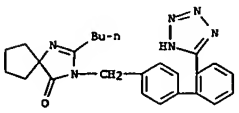
RN 745814-09-9 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-(1,1-dimethylethyl)-3-[[2'-(1-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:633925 CAPLUS
DOCUMENT NUMBER: 141:157121
TITLE: Synthesis of irbesartan
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-zion
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

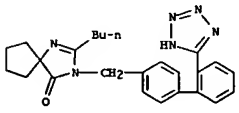
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004065383	A2	20040805	WO 2004-US1135	20040116
WO 2004065383	A3	20041216		
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ				
US 2004192713	A1	20040930	US 2004-759906	20040116
EP 1509517	A2	20050302	EP 2004-702955	20040116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2003-440997P P 20030116
WO 2004-US1135 W 20040116
OTHER SOURCE(S): CASREACT 141:157121
AB Provided are a method of making irbesartan via a Suzuki coupling reaction and a novel intermediate, 2-butyl-3-(4'-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one, for such process. The novel process includes the step of reacting such intermediate with a protected tetrazolylphenylboronic acid.
IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of irbesartan)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:594584 CAPLUS
DOCUMENT NUMBER: 142:32318
TITLE: AT1 receptor antagonists: pharmacology
AUTHOR(S): de Gasparo, M.
CORPORATE SOURCE: MG Consulting Co, Rossemaison, 2842, Switz.
SOURCE: Handbook of Experimental Pharmacology (2004), 163/II(Angiotensin, Volume 2), 417-451
CODEN: HEPHD2; ISSN: 0171-2004
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Innovative chemical modifications of the first nonpeptide imidazole antagonist of Ang II led to the synthesis of various new orally active agents with increased potency and improved bioavailability (13%-80%). They block specifically and selectively the angiotensin AT1 receptor without intrinsic agonist properties. The angiotensin receptor blockers (ARB) can be classified as surmountable, (losartan, eprosartan, telmisartan), insurmountable (candesartan) or mixed (valsartan, irbesartan, olmesartan) antagonists depending on their degree of tight binding and their dissociation rate. Candesartan and olmesartan are administered as prodrug converted to the active compound upon absorption. The ARBs are excreted essentially in the bile and mainly unchanged. If biotransformed, it involves oxidative reaction and conjugation. The metabolism of irbesartan, losartan, and candesartan requires cytochrome P 450 enzymes. There is no accumulation by repeated doses. Plasma concns. are little influenced by mild-to-moderate renal impairment but caution may be required in patients with hepatic insufficiency due to the biliary mechanism of excretion. Losartan is unique by its uricosuric property. In general, the ARBs do not interfere with other drugs in a clin. significant way, but caution should be taken if prescribed with potassium-sparing agents or supplements, especially in elderly patients with reduced renal function. The ARBs are generally well tolerated with an incidence of adverse effects or withdrawals similar to the placebo. First-dose hypotension is uncommon and there is no rebound hypertension after withdrawal. Angio-edema is rare. The ARBs are contra-indicated during pregnancy. The efficacy of the ARBs in hypertension is well documented in various population and age groups and better tolerated than other antihypertensive agents for similar efficacy. The first properly powered trial in an hypertensive population, LIFE with losartan, has demonstrated a beneficial effect on the primary composite endpoint, including cardiovascular death, myocardial infarction and stroke, even more impressive in a diabetic subgroup. Based on the result of Val-HeFT, valsartan is approved in heart failure patients intolerant to ACE inhibitor. The renoprotective effect of the ARBs was demonstrated in diabetic nephropathy with irbesartan, losartan and valsartan. Various clin. studies suggest a beneficial effect of the ARBs beyond the blood pressure fall. Several large trials are in progress to establish the efficacy of the ARBs in patients with LV dysfunction following recent myocardial infarction. As blockade of the AT1 receptor is accompanied by increased plasma Ang II, the potential of the stimulation of the unblocked AT2 receptor is discussed. Possible further indications for ARB are also briefly reported.
IT 138402-11-6, Irbesartan
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mixed ARB irbesartan requires cytochrome P 450 enzymes for metabolism and

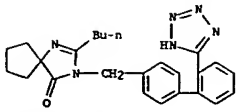
L5 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
has renoprotective effect in diabetic nephropathy)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 186 THERE ARE 186 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:475010 CAPLUS
DOCUMENT NUMBER: 141:405861
TITLE: Effect of irbesartan on angiotensin II-induced hypertrophy of human proximal tubular cells
AUTHOR(S): Liu, Bi-cheng; Sun, Jing; Chen, Qi; Luo, Dong-dong; Ma, Kun-ling; Ruan, Xiong-zhong
CORPORATE SOURCE: Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing, 210009, Peop. Rep. China
SOURCE: Chinese Medical Journal (Beijing, China, English Edition) (2004), 117(4), 547-551
CODEN: CMJODS; ISSN: 0366-6999
PUBLISHER: Chinese Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Intrarenal activation of the renin angiotensin system (RAS) plays an important role in mediating renal fibrosis. Both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II (Ang II) receptor antagonists have been shown to exert a protective role against diabetic and non-diabetic nephropathy. However, the exact mechanism of how blocking local RAS prevents renal fibrosis is unclear. The present study was to investigate the influence of a new Ang II receptor antagonist, irbesartan (Irb), on Ang II-induced hypertrophy in human proximal tubular cell line (HK-2). Methods: The cell line, HK-2, was grown in Dulbeccos's Modified Eagle's Medium containing 10% heat-inactivated fetal calf serum. After rested in serum-free medium for 24 h, the effects of Irb on Ang II (10-7 mol/L)-induced [3H]-leucine incorporation, total protein content (measured by the Coomassie brilliant blue G250 method), and change in cell size (determined by SEM) were observed The influence of Irb on the cell cycle was analyzed by fluorescence activated cell sorter (FACS) flow cytometry. Results: Ang II induced cell hypertrophy in a time and dose dependent manner. Stimulation of cells with Ang II for 48 h resulted in a increase in [3H]-leucine incorporation [0 h; (5584 ± 1016) cpm/105 cells vs 48 h; (10741 ± 802) cpm/105 cells, P < 0.05], which was significantly attenuated by treatment with Irb. Ang II significantly increased the total protein content in HK-2 cells [control: (0.169 ± 0.011) mg/105 cells vs Ang II group; (0.202 ± 0.010) mg/105 cells, P<0.05], which was also markedly inhibited by cotreatment with Irb (P < 0.01). SEM showed that Ang II induced an increase in average phys. cell size, which was significantly inhibited by Irb [control; (11.92 ± 1.62) μm; Ang II group; (20.63 ± 3.83) μm; Ang II + Irb group: (13.59 ± 3.15) μm; P < 0.01 vs control, resp.]. Furthermore, flow cytometry revealed that Ang II arrested cells in the G0-G1 phase, which was significantly reversed by treatment with Irb [G0-G1 cells in Ang II group; (76.09±1.82)%, in Ang II + Irb group; (67.00 ± 2.52)%, P<0.05]. Conclusion: Irb can inhibit Ang II-induced hypertrophy in HK-2 cells.
IT 138402-11-6, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin II receptor antagonist irbesartan inhibited Ang II-induced hypertrophy of human proximal tubular HK-2 cell line)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:451474 CAPLUS
DOCUMENT NUMBER: 141:1258
TITLE: Nitrosated compounds in methods of treating vascular diseases characterized by nitric oxide insufficiency
INVENTOR(S): Loscalzo, Joseph; Vita, Joseph A.; Loberg, Michael D.; Worcel, Manuel
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 679,257.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004105850	A1	20040603	US 2003-692724		20031027
US 6635273	B1	20031021	US 2000-697317		20001027
US 2004071766	A1	20040415	US 2003-679257		20031007
PRIORITY APPLN. INFO.:			US 1999-162230P	P	19991029
			US 2000-179020P	P	20000131
			US 2000-697317	A1	20001027
			US 2003-679257	A2	20031007

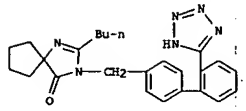
OTHER SOURCE(S): MARPAT 141:1258

AB The invention provides methods of treating and/or preventing vascular diseases characterized by nitric oxide insufficiency by administering a therapeutically effective amount of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, and optionally at least one compound used to treat cardiovascular diseases and/or at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The antioxidant may preferably be a hydralazine compound or a pharmaceutically acceptable salt thereof. The compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase may preferably be isosorbide dinitrate and/or isosorbide mononitrate. The vascular diseases characterized by nitric oxide insufficiency include a cardiovascular disease and a disease resulting from oxidative stress. Nitric oxide action was shown to be impaired in the microvasculature of black hypertensive patients to a greater extent than in white hypertensive patients.

IT 138402-11-6D, Irbesartan, nitrosated compds.
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



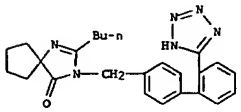
L5 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:404854 CAPLUS
DOCUMENT NUMBER: 140:417642
TITLE: Diverse effects of long-term treatment with imidapril and irbesartan on cell growth signal, apoptosis and collagen type I expression in the left ventricle of spontaneously hypertensive rats
AUTHOR(S): Wang, Jin-ming; Wang, Ying; Zhu, Zhong-sheng; Zhang, Mei-chun; Zou, Yi; Li, Jian-jun; Li, Ming-jiang; Jiang, Xue-jun; Li, Xiao-Yan
CORPORATE SOURCE: Renmin Hospital, Department of Cardiology, Wuhan University School of Medicine, Wuhan, 430060, Peop. Rep. China
SOURCE: Life Sciences (2004), 75(4), 407-420
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To compare diverse effects of angiotensin II type 1 receptor antagonists (irbesartan) and angiotensin converting enzyme inhibitors (imidapril) on left ventricular remodeling in spontaneously hypertensive rats (SHR). Thirty male SHR were randomly divided into three groups: SHR-IR (treated with irbesartan, 50 mg/kg), SHR-IM (imidapril, 3 mg/kg), SHR-C (placebo). Ten male Wistar Kyoto rats (WKY) treated with placebo acted as the control. All treatments were administered once daily from 14 to 27 wk of age. Imidapril and irbesartan have the similar inhibitor effects on blood pressure and left ventricular mass indexes in SHR. Despite both drugs suppressed ERK-1 protein expression, decreased cardiomyocytes apoptosis index, blocked collagen type I deposition, reduced TGF-β1 gene expression in SHR, imidapril elicits a stronger inhibitory effect. Irbesartan had little effect on MKP-1 protein expression, but imidapril decreased it significantly. As a result, the ERK-1/MKP-1 ratio in SHR-IR was significantly greater than that in SHR-IM ($P < 0.05$). These results suggest that the balance between MKP-1 and ERKs in myocardial tissue is important for cardiac cell proliferation and growth. They also indicate that the similar efficacy of antihypertensive treatment in reducing blood pressure does not predict the similar capacity to control the individual facet of left ventricular remodeling. Irbesartan is more effective in regressing the homeostasis between ERK-1 and MKP-1, however imidapril is superior in suppressing apoptosis and collagen synthesis in cardiac tissue.

IT 138402-11-6, Irbesartan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diverse effects of long-term treatment with imidapril and irbesartan on cell growth signal, apoptosis and collagen I in left ventricle in hypertension)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:392331 CAPLUS
DOCUMENT NUMBER: 140:406798
TITLE: Preparation of benzoxepinopyridines as HMG-CoA reductase inhibitors
INVENTOR(S): Robl, Jeffrey A.; Chen, Bang-chi; Sun, Chong-qing
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: U.S. Pat. Appl. Publ., 44 pp., Cont.-in-part of U.S. Ser. No. 875,155, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004092573	A1	20040513	US 2003-602752	20030624
US 6812345	B2	20041102		
US 2002013334	A1	20020131	US 2001-875155	20010606
PRIORITY APPLN. INFO.:			US 2000-211595P	P 20000615
			US 2001-875155	B2 20010606

OTHER SOURCE(S): MARPAT 140:406798
GI

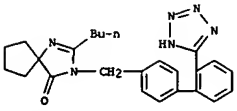
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [X = O, S, SO, SO2, NR7; Z = HOCHCH2CH(OH)CH2CO2R3, 4-hydroxy-2-oxopyran-6-yl, etc.; n = 0, 1; R1, R2 = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, cycloheteroalkyl; R3 = H, alkyl, metal ion; R4 = H, halo, CF3, etc.; R7 = H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, etc.; R9, R10 = H, alkyl], were prepared as HMG CoA reductase inhibitors active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing HDL cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis (no data). A multistep synthesis of II is reported.

IT **138402-11-6**, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministered agents; preparation of benzoxepinopyridines as HMG-CoA reductase inhibitors for treatment of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, and other disorders)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

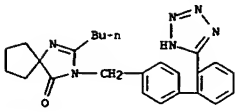
ACCESSION NUMBER: 2004:292572 CAPLUS
DOCUMENT NUMBER: 141:16887
TITLE: Novel dual action AT1 and ETA receptor antagonists reduce blood pressure in experimental hypertension
AUTHOR(S): Kowala, Mark C.; Murugesan, Natesan; Tellew, John; Carlson, Kenneth; Monshizadegan, Hossain; Ryan, Carol; Gu, Zhengxiang; Kane, Bridgette; Fadnis, Leena; Baska, Rose Ann; Beyer, Sophie; Arthur, Susan; Dickinson, Kenneth; Zhang, Donglu; Perrone, Mark; Ferrer, Pam; Giancarli, Mary; Baumann, Jergen; Bird, Eileen; Panchal, Balkrushna; Yang, Yifan; Trippodo, Nick; Barrish, Joel; Macor, John E.
CORPORATE SOURCE: Departments of Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2004), 309(1), 275-284
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiotensin II and endothelin-1 activate their resp. AT1 and ETA receptors on vascular smooth muscle cells, producing vasoconstriction, and both peptides are implicated in the pathogenesis of essential hypertension. Angiotensin II potentiates the production of endothelin, and conversely endothelin augments the synthesis of angiotensin II. Both AT1 and ETA receptor antagonists lower blood pressure in hypertensive patients; thus, a combination AT1/ETA receptor antagonist may have greater efficacy and broader utility compared with each drug alone. By rational drug design a biphenyl ETA receptor blocker was modified to acquire AT1 receptor antagonism. These compds. (C and D) decreased Sar-Ile-Angiotensin II binding to AT1 receptors and endothelin-1 binding to ETA receptors, and compound C inhibited angiotensin II- and endothelin-1-mediated Ca2+ transients. In rats compds. C and D reduced blood pressure elevations caused by i.v. infusion of angiotensin II or big endothelin-1. Compound C decreased blood pressure in Na+-depleted spontaneously hypertensive rats and in rats with mineralocorticoid hypertension. Compound D was more efficacious than AT1 receptor antagonists at reducing blood pressure in spontaneously hypertensive rats, and its superiority was likely due to its partial blockade of ETA receptors. Therefore compds. C and D are novel agents for treating a broad spectrum of patients with essential hypertension and other cardiovascular diseases.

IT **138402-11-6**, Irbesartan
RL: PAC (Pharmacological activity); BIOL (Biological study)
(novel dual action AT1 and ETA receptor antagonists reduce blood pressure in exptl. hypertension)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 17 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



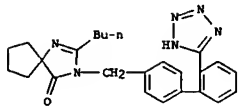
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:60496 CAPLUS
DOCUMENT NUMBER: 140:111420
TITLE: Synthesis of irbesartan
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-Zion; Shapiro, Eugeny; Yahalomi, Bonit
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004007482	A2	20040122	WO 2003-US22479	20030716
WO 2004007482	A3	20040527		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2492779	AA	20040122	CA 2003-2492779	20030716
EP 1546135	A2	20050629	EP 2003-764805	20030716
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005176794	A1	20050811	US 2003-621623	20030716
PRIORITY APPLN. INFO.:			US 2002-396424P P	20020716
			US 2002-402490P P	20020809
			WO 2003-US22479 W	20030716

OTHER SOURCE(S): CASREACT 140:111420
AB Irbesartan is prepared by reaction of 2-butyl-1,3-diaza-spiro[4.4]non-1-ene (I) with 5-(4-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole (II) in the presence of a phase transfer catalyst. Thus, reaction of I with II in toluene in the presence of Bu4NHSO4 at 90° for 1.5 h gave, after deprotection, 84.3% irbesartan. Also provided is irbesartan having a fine particle size.
IT **138402-11-6P**, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of irbesartan)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

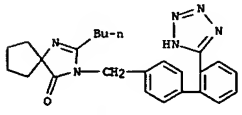
L5 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L5 ANSWER 19 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:696766 CAPLUS
DOCUMENT NUMBER: 139:207790
TITLE: Antihypertensive composition and method using an antihypertensive agent-antiinflammatory agent combination
INVENTOR(S): Hamet, Pavel; Tremblay, Johanne
PATENT ASSIGNEE(S): Corporation du Centre de Recherche du Chum, Can.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072136	A1	20030904	WO 2003-CA266	20030226
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2002-359331P P	20020226

AB A method and compns. are provided for attenuating and/or preventing blood pressure increment caused by a stressful stimuli. The method consists in administering to a mammal a composition including an effective amount of at least one antihypertensive compound in combination with an effective amount of at least one antiinflammatory agent.
IT **138402-11-6**, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive agent-antiinflammatory agent combination for stress-caused hypertension)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



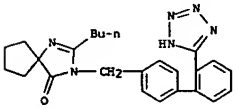
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:587858 CAPLUS
DOCUMENT NUMBER: 137:288496
TITLE: Discovery of N-isoxazolyl biphenylsulfonamides as potent dual angiotensin II and endothelin A receptor antagonists
AUTHOR(S): Murugesan, Natesan; Tellew, John E.; Gu, Zhengxiang; Kunst, Bridgette L.; Fadnis, Leena; Cornelius, Lyndon A.; Baska, Rose Ann F.; Yang, Yifan; Beyer, Sophie M.; Monshizadegan, Hossain; Dickinson, Kenneth E.; Panchal, Balkrushna; Valentine, Maria T.; Chong, Saeho; Morrison, Richard A.; Carlson, Kenneth E.; Powell, James R.; Moreland, Suzanne; Barrish, Joel C.; Kowala, Mark C.; Macor, John E.
CORPORATE SOURCE: Discovery Chemistry and Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-5400, USA
SOURCE: Journal of Medicinal Chemistry (2002), 45(18), 3829-3835
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:288496

AB The ETA receptor antagonist N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)-[1,1'-biphenyl]-2-sulfonamide (BMS-193884) shares the same biphenyl core as a large number of AT1 receptor antagonists, including irbesartan. Thus, it was hypothesized that merging the structural elements of BMS-193884 with those of the biphenyl AT1 antagonists (e.g., irbesartan) would yield a compound with dual activity for both receptors. This strategy led to the design, synthesis, and discovery of 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-[1,1'-biphenyl]-2-sulfonamide (BMS-248360) as a potent and orally active dual antagonist of both AT1 and ETA receptors. Compound BMS-248360 represents a new approach to treating hypertension.

IT 138402-11-6, Irbesartan
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(discovery of N-isoxazolyl biphenylsulfonamides as potent dual angiotensin II and endothelin A receptor antagonists)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



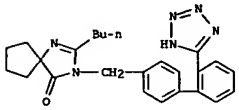
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:569152 CAPLUS
DOCUMENT NUMBER: 138:104378
TITLE: Forefront of diabetes and renal diseases
AUTHOR(S): Kamiya, Yoshinobu; Kimura, Genjiro
CORPORATE SOURCE: Graduate School of Medicine, Nagoya City University, Japan
SOURCE: Bunshi Shin Kekkanbyo (2002), 3(2), 209-215
CODEN: BSKUAB; ISSN: 1345-2355
PUBLISHER: Sentan Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review on role of angiotensin II in diabetic nephropathy. The topics discussed are (1) renal renin-angiotensin system in diabetic nephropathy; (2) glucose-induced angiotensin II in mesangial cells; (3) glucose and angiotensin II in stimulating extracellular matrix protein synthesis through induction of transforming growth factor-β expression; (4) association of genetic polymorphisms of proteins in renin-angiotensin system with diabetic nephropathy; and (5) effects of angiotensin II receptor blockers losartan and irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.

IT 138402-11-6, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin II and its receptor in diabetic nephropathy and role of angiotensin receptor antagonists)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:540258 CAPLUS
DOCUMENT NUMBER: 137:109267
TITLE: Preparation of benzoxepinopyridines as HMG-CoA reductase inhibitors
INVENTOR(S): Robl, Jeffrey A.; Chen, Bang-chi; Sun, Chong-qing
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp., Cont.-in-part of U.S. Ser. No. 875,155.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002094977	A1	20020718	US 2001-7407	20011204
US 6627636	B2	20030930		
US 2002013334	A1	20020131	US 2001-875155	20010606
PRIORITY APPLN. INFO.:			US 2000-211595P	P 20000615
			US 2001-875155	A2 20010606

OTHER SOURCE(S): MARPAT 137:109267
GI

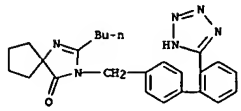
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [X = O, S, SO, SO2, NR7; Z = HOCHCH2CH(OH)CH2CO2R3, 4-hydroxy-2-oxopyran-6-yl, etc.; n = 0, 1; R1, R2 = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, cycloheteroalkyl; R3 = H, alkyl, metal ion; R4 = H, halo, CF3, etc.; R7 = H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, etc.; R9, R10 = H, alkyl], were prepared as HMG CoA reductase inhibitors active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing HDl cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis (no data). A multistep synthesis of II is reported.

IT 138402-11-6, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministered agents; preparation of benzoxepinopyridines as HMG-CoA reductase inhibitors for treatment of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, and other disorders)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-{[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

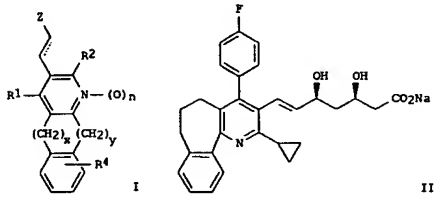
L5 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L5 ANSWER 23 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:392237 CAPLUS
DOCUMENT NUMBER: 136:401651
TITLE: Preparation of fused pyridine derivatives as HMG-CoA reductase inhibitors
INVENTOR(S): Robl, Jeffrey A.; Chen, Bang-Chi; Sun, Chong-Qing
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 875,218.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002061901	A1	20020523	US 2001-8154	20011204
US 6620821	B2	20030916		
US 2002028826	A1	20020307	US 2001-875218	20010606
US 2004024216	A1	20040205	US 2003-602753	20030624
PRIORITY APPLN. INFO.:			US 2000-211594P	P 20000615
			US 2001-875218	A2 20010606
			US 2001-8154	A3 20011204

OTHER SOURCE(S): MARPAT 136:401651
GI



I II

AB The title compds. I and their pharmaceutically acceptable salts, esters, prodrug esters, and stereoisomers are claimed [wherein: Z = CH(OH)CH2CR7(OH)CH2CO2R3 or corresponding pyranone lactone derivs.; n = 0, 1; x = 0, 1, 2, 3, or 4; y = 0, 1, 2, 3 or 4, provided that at least one of x and y is other than 0; and optionally one or more carbons of (CH2)x and/or (CH2)y together with addnl. carbons form a 3 to 7 membered spirocyclic ring; R1, R2 = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, cycloheteroalkyl; R3 = H or lower alkyl; R4 = H, halo, CF3, OH, alkyl, alkoxy, CO2H, (un)substituted NH2, cyano, (un)substituted CONH2, etc.; R7 = H, alkyl]. The compds. are HMG-CoA reductase inhibitors, and are active in inhibiting cholesterol biosynthesis and modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol (no data). I are thus useful in treating hyperlipidemia and dyslipidemia, in hormone replacement therapy, and in treating hypercholesterolemia, hypertriglyceridemia and atherosclerosis, as well as Alzheimer's disease and osteoporosis. Prepns.

L5 ANSWER 24 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:315368 CAPLUS
DOCUMENT NUMBER: 136:330577
TITLE: Tissue perfusion enhancement by co-administration of a drug that increases cGMP synthesis and an agent that inhibits cGMP degradation
INVENTOR(S): Mueller, Thomas H.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 3 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

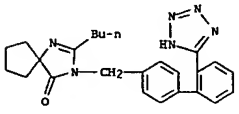
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002048599	A1	20020425	US 2001-981335	20011016
WO 2002034248	A2	20020502	WO 2001-US42742	20011016
WO 2002034248	A3	20030403		

W: CA, JP, MX
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
PRIORITY APPLN. INFO.: US 2000-242342P P 20001020

AB A method for increasing tissue perfusion with blood by the co-administration of an agent that increases cGMP synthesis and an agent that inhibits cGMP degradation in the cells of the blood vessel walls or in blood cells. The method comprises, for example, the co-administration of a statin and dipyridamole, especially a timed-release formulation of dipyridamole. Atorvastatin at 5-80 or fluvastatin at 10-40 mg/day can be used.

IT 138402-11-6, Irbesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tissue perfusion enhancement by co-administration of drugs that increase cGMP synthesis)

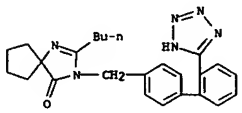
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 23 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
of several compds. are described. For instance, a multistep synthesis of fused pyridine deriv. II is reported. Compds. I may be used in a manner similar to atorvastatin, pravastatin, simvastatin, etc. Combinations of compds. I with various other drugs are claimed, the latter being specified as certain pharmacol. classes, as inhibitors of specific enzymes, as (ant)agonists of specific receptors, and as numerous named drugs.

IT 138402-11-6, Irbesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. also containing; preparation of fused pyridine derivs. as HMG-CoA reductase inhibitors)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



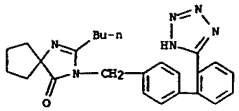
L5 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:203409 CAPLUS
DOCUMENT NUMBER: 136:353534
TITLE: Lack of impairment of nitric oxide-mediated responses in a rat model of high-renin hypertension
AUTHOR(S): Artigues-Varin, C.; Richard, V.; Renet, S.; Henry, J. P.; Thuillez, C.
CORPORATE SOURCE: Department of Pharmacology, INSERM EMI 9920, IFRMP no 23, Rouen University Medical School, Rouen, 76183, Fr.
SOURCE: Clinical and Experimental Pharmacology and Physiology (2002), 29(1/2), 26-31
CODEN: CEXPB9; ISSN: 0305-1870
PUBLISHER: Blackwell Publishing Asia
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1. Angiotensin (Ang) II triggers the expression of a prooxidant phenotype in the vascular wall, suggesting that activation of the renin-angiotensin system (RAS) causes endothelial dysfunction in various pathol. situations, such as hypertension. However, this hypothesis has been mostly tested in a setting of exogenous administration of AngII. 2. We tested the hypothesis of a role for endogenous activation of the RAS leading to oxidant stress and endothelial dysfunction in a high-renin model of hypertension (i.e. two-kidney, one-clip hypertension) in rats. One month after clipping or sham surgery, aorta were isolated from untreated rats or rats treated by the angiotensin AT1 receptor antagonist irbesartan (10 mg/kg per day). Mesenteric artery segments were also isolated from normotensive or hypertensive rats. 3. Hypertension reduced the relaxations to acetylcholine but did not affect the ratio of contractions to phenylephrine in the presence compared with the absence of a nitric oxide (NO) synthase inhibitor, used as an index of basal release of NO. 4. The free radical scavenger tempol reduced the contractions to phenylephrine in the absence, but not in the presence, of an inhibitor of NO synthesis. This index of free radical-mediated degradation of NO was not affected by hypertension. In parallel, hypertension did not affect the expression of p22phox, a component of the free radical generating enzyme reduced NADP oxidase. 5. Chronic treatment with the AT1 receptor antagonist decreased blood pressure, moderately improved the response to acetylcholine, but did not affect basal NO release in hypertensive rats, although it did increase basal NO release in normotensive rats. 6. Thus, this model of hypertension is characterized by an impaired stimulated NO release but not of basal NO release in isolated arteries. Furthermore, there was no functional evidence of an increased oxidative stress-mediated impairment of NO release. This is not in favor of a direct link between activation of the RAS and development of endothelial dysfunction in exptl. hypertension.

IT 138402-11-6, Irbesartan
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lack of impairment of nitric oxide-mediated responses in a rat model of high-renin hypertension)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

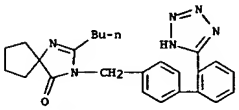
L5 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:426040 CAPLUS
DOCUMENT NUMBER: 135:283303
TITLE: **Synthesis** and study of a cyclic angiotensin II antagonist analogue reveals the role of π'-π' interactions in the C-terminal aromatic residue for agonist activity and its structure resemblance with AT1 non-peptide antagonists
AUTHOR(S): Polevaya, L.; Mavromoustakos, T.; Zoumboulakis, P.; Grdadolnik, S. G.; Roumelioti, P.; Giatas, N.; Mutule, I.; Keivish, T.; Vlahakos, D. V.; Iliodromitis, E. K.; Kremastinos, D. Th.; Matsoukas, J.
CORPORATE SOURCE: Laboratory of Peptide Chemistry, Latvian Institute of Organic Synthesis, Riga, LV-1006, Latvia
SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(6), 1639-1647
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The novel amide linked Angiotensin II (ANG II) cyclic analog cyclo(3,5)-[Sar1-Lys3-Glu5-Ile8] ANG II (18) has been designed, **synthesized** and bioassayed in anesthetized rabbits. The constrained cyclic analog with a lactam amide bridge linking a Lys-Glu pair at positions 3 and 5 and possessing Ile at position 8, was **synthesized** by solution procedure using the maximum protection strategy. This analog was found to be inhibitor of Angiotensin II. NMR spectroscopy coupled with computational anal. showed clustering between the side chains of the key amino acids Tyr4-His6-Ile8 similar to that observed with ANG II. The obtained data show that only π'-π' interactions observed in ANG II or its superagonist Sar1 [ANG II] are missing. Therefore, it can be concluded that these interactions are essential for agonist activity. Conformational anal. comparisons between AT1 antagonists losartan, eprosartan and irbesartan with C-terminal segment of cyclic compound 18 revealed structural similarities.

IT 138402-11-6, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**synthesis** of a cyclic angiotensin II antagonist analog reveals role of π'-π' interactions in C-terminal aromatic residue for agonist activity and structure resemblance with AT1 non-peptide antagonists)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

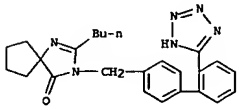
L5 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:405278 CAPLUS
DOCUMENT NUMBER: 136:183766
TITLE: Improvement on synthetic technology of irbesartan
AUTHOR(S): Shen, Jingshan; Yan, Tiema; Li, Huijun; Li, Jianfeng; Lei, Lijun; Ji, Ruyun
CORPORATE SOURCE: Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE: Zhongguo Yaowu Huaxue Zazhi (2001), 11(2), 104-106
CODEN: ZYHZEF; ISSN: 1005-0108
PUBLISHER: Zhongguo Yaowu Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 136:183766

AB Two methods for **synthesizing** irbesartan were presented. Irbesartan was prepared from 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (I) and 4-bromomethyl-2'-cyanobiphenyl by substitution and cyclization with a good yield of 63%. It can also be obtained from I and 2-(4'-bromo-1,1'-biphenyl-2-yl)-2-triphenylmethyltetrazole through substitution and deprotection with overall yield of 85%. The structure was confirmed by 1H-NMR and MS.

IT **138402-11-6P**, Irbesartan
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**synthesis** of irbesartan)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

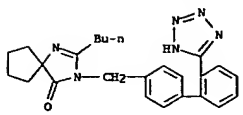
ACCESSION NUMBER: 2001:323259 CAPLUS
DOCUMENT NUMBER: 135:267028
TITLE: Renal safety of combined cyclooxygenase 2 (COX-2) inhibitor and angiotensin II receptor blocker administration in mild volume depletion
AUTHOR(S): Kistler, Thomas; Ambuhl, Patrice M.
CORPORATE SOURCE: Renal Division, University Hospital, Zurich, Switz.
SOURCE: Swiss Medical Weekly (2001), 131(13/14), 193-198
CODEN: SMWWAI; ISSN: 1424-7860
PUBLISHER: EMH Swiss Medical Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Principles: Drugs that either inhibit prostaglandin synthesis or antagonize angiotensin II effects are likely to impair renal function, especially in patients with an activated renin-angiotensin-aldosterone system.

Of the former, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used, and newer agents with cyclooxygenase 2 (COX-2) specific inhibition may have fewer renal side effects compared to non-selective NSAIDs. We therefore investigated whether combination of a COX-2 inhibitor with an angiotensin II subtype 1 (AT1) receptor blocker is safe with regard to preservation of normal renal function in a state of slight volume contraction. Methods: Mild volume depletion was induced by a salt-restricted diet in 5 healthy volunteers who were then given a single dose of 400 mg celecoxib, a COX-2 inhibitor, alone or in combination with 150 mg irbesartan, an AT1 receptor blocker. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by measuring inulin and PAH clearance resp., along with plasma renin activity (PRA) and urinary electrolyte excretion before and over 100 min after drug administration. Results: PRA was high prior to drug administration, indicating slight salt depletion, and dropped by 65% after intake of celecoxib alone (p = 0.008) but only by 25% after combined intake with irbesartan (p = n.s.). GFR was not affected either by celecoxib alone or by combined administration with irbesartan. In contrast, ERPF increased by 28% 80 min after simultaneous drug intake (p = 0.029), but not after celecoxib alone. Renal sodium and potassium excretion did not significantly change under celecoxib alone or in combination with irbesartan. Conclusion: Selective COX-2 inhibition by celecoxib in combination with an AT1 receptor blocker (irbesartan) has no acute adverse effects on renal hemodynamics and renal salt handling in slightly volume-depleted subjects with normal renal function. Moreover, our data obtained in humans appear to confirm the co-regulatory interaction of COX-2 and angiotensin II in the control of renin release, as suggested by animal studies.

IT 138402-11-6, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(renal safety of combined cyclooxygenase 2 (COX-2) inhibitor and angiotensin II receptor blocker administration in mild volume depletion)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L5 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:283949 CAPLUS
DOCUMENT NUMBER: 134:311218
TITLE: Synthesis and use of heterocyclic sodium/proton exchange inhibitors
INVENTOR(S): Ahmad, Saleem; Wu, Shung C.; O'Neil, Steven V.; Ngu, Khehyong; Atwal, Karnail S.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 221 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001027107	A2	20010419	WO 2000-US27461	20001002
WO 2001027107	A3	20020124		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6887870	B1	20050503	US 2000-669298	20000925
CA 2388813	AA	20010419	CA 2000-2388813	20001002
EP 1224183	A2	20020724	EP 2000-968723	20001002
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
BR 2000014725	A	20030617	BR 2000-14725	20001002
JP 2003527331	T2	20030916	JP 2001-530325	20001002
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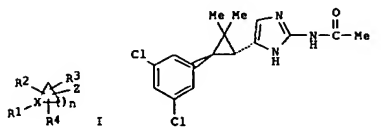
ZA 2002002479	A	20040727	ZA 2002-2479	20020327
NO 2002001717	A	20020610	NO 2002-1717	20020411
US 2005137216	A1	20050623	US 2005-46993	20050131

PRIORITY APPLN. INFO.: US 1999-158755P P 19991012
US 2000-669298 A3 20000925
WO 2000-US27461 W 20001002

OTHER SOURCE(S): MARPAT 134:311218
GI

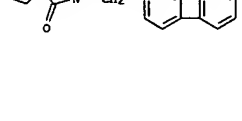


AB Compds. of formula I [wherein; n is 1-5; X is N or CR5, where R5 is H, halo, alkenyl, alkynyl, alkoxy, alkyl, aryl or heteroaryl; Z is a heteroaryl group; R1 is H, alk(en)(yn)yl, alk(enyl)(ynyl)oxy, (aryl or

L5 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

alkyl)3Si, cycloalk(en)yl, (aryl)amino, aryl(alkyl), cycloheteroaryl, etc.; R2, R3 and R4 are any of the groups set out for R1 and optionally substituted with 1 to 5 substituents which may be the same or different and when X is N, R1 is preferably aryl or heteroaryl] are claimed. Several hundred examples are disclosed. Synthesis of II proceeds via cyclopropanation of the cinnamate derived from the olefination between 3,5-dichlorobenzaldehyde and t-butyldiethylphosphonoacetate. The intermediate tert-Bu ester is converted to the corresponding α-chloroketone and reacted with acetyl guanidine to provide II in a total of 5 steps. Compds. I are said to be sodium/proton exchange inhibitors (NHE). Pharmaceutical combinations are claimed using I and certain antihypertensive agents, β-adrenergic agonists, hypolipidemic agents, antidiabetic agents, antiobesity agents, etc. Compds. I are useful as antianginal and cardioprotective agents and provide a method for preventing or treating angina pectoris, cardiac dysfunction, myocardial necrosis, and arrhythmia.

IT 138402-11-6, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceuticals also containing; synthesis and use of heterocyclic sodium/proton exchange inhibitors)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



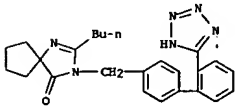
L5 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:79544 CAPLUS
DOCUMENT NUMBER: 134:261085
TITLE: ACE inhibitor and AT1 antagonist blockade of deformation-induced gene expression in the rabbit jugular vein through B2 receptor activation
AUTHOR(S): Lauth, Manfred; Cattaruzza, Marco; Hecker, Markus
CORPORATE SOURCE: Department of Cardiovascular Physiology, University of Gottingen, Gottingen, 37073, Germany
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2001), 21(1), 61-66
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Deformation-induced endothelin-1 synthesis in endothelial cells may contribute to the intimal hyperplasia of venous bypass grafts. ACE inhibitors and angiotensin II type 1 (AT1) receptor antagonists are capable of reducing vein graft disease. Therefore, the effects of these drugs on endothelial preproendothelin-1 (ppET-1) and smooth muscle endothelin B receptor (ETB-R) expression were investigated in isolated perfused segments of the rabbit jugular vein. Pretreatment with ramiprilat (0.3 μmol/L) or irbesartan (0.01 to 1 μmol/L) had no effect on basal ppET-1 or ETB-R expression but markedly attenuated the deformation-induced expression of these gene products, and these effects were reversed by the B2 receptor antagonist icatibant (Hoe 140) and by the NO synthase inhibitor NG-nitro-L-arginine. Candesartan (1 μmol/L) mimicked the inhibitory effect of irbesartan. Moreover, reporter gene anal. with a rat ppET-1 promoter-luciferase construct transiently transfected into porcine aortic cultured endothelial cells revealed that the inhibitory effect of both ramiprilat and irbesartan on deformation-induced ppET-1 expression is species independent and mediated at the level of transcription. In addition, RT-PCR anal. detected only AT1 receptor expression in the endothelium-intact rabbit jugular vein, and neither irbesartan nor ramiprilat affected endothelial NO synthase expression. Thus, ACE inhibitors and AT, receptor antagonists are capable of suppressing deformation-induced gene expression in the vessel wall in both an autocrine (ppET-1) and a paracrine (ETB-R) manner via a common mechanism of action that constitutes a B2 receptor-mediated increase in endothelial NO release.

IT 138402-11-6, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACE inhibitor and AT1 antagonist blockade of deformation-induced gene expression in jugular vein through B2 receptor activation)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

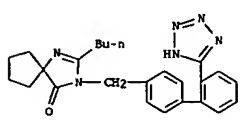
L5 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:470756 CAPLUS
DOCUMENT NUMBER: 133:222649
TITLE: Synthesis and Pharmacological Evaluation of New Pyrazolidine-3,5-diones as AT1 Angiotensin II Receptor Antagonists
AUTHOR(S): Le'Bourdonnec, Bertrand; Meulon, Emmanuelle; Yous, Saied; Goossens, Jean-Francois; Houssin, Raymond; Henichart, Jean-Pierre
CORPORATE SOURCE: Institut de Chimie Pharmaceutique Albert Lespagnol and Laboratoire de Chimie Analytique Faculte des Sciences Pharmaceutiques et Biologiques, Universite de Lille 2, Lille, F-59006, Fr.
SOURCE: Journal of Medicinal Chemistry (2000), 43(14), 2685-2697
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB On the basis of the structure of the non-peptide receptor antagonist irbesartan, a new series of AT1 ligands was designed. In these compds. the central imidazolone nucleus of irbesartan was replaced by a pyrazolidine-3,5-dione structure. The key intermediate N-alkylpyrazolidine-3,5-diones were synthesized according to a new and general method. The most active compds. possess a spirocyclopentane ring at position 4, a linear Bu chain at position 1, and the [2'-(5-tetrazolyl)biphenyl-4-yl]methyl or [2'-(benzoylaminosulfonyl)biphenyl-4-yl]methyl group at position 2. Affinity toward the AT1 and AT2 receptors was assessed by the ability of the compds. to competitively displace [3H]AII from its specific binding sites. The most active compds., 2-butyl-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-2,3-diazaspiro[4.4]nonane-1,4-dione and N-[4-[[[3-butyl-1,4-dioxo-2,3-diazaspiro[4.4]non-2-yl]methyl]-[1,1'-biphenyl]-2-yl]sulfonyl]benzamide, displayed high affinity for the AT1 receptor, good selectivity AT1 vs. AT2, and potent in vitro antagonist activity.

IT 138402-11-6DP, Irbesartan, derivs. and analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and activity of pyrazolidinediones as AT1 angiotensin II receptor antagonists)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:113674 CAPLUS
DOCUMENT NUMBER: 130:168359
TITLE: Preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls
INVENTOR(S): Castro, Bertrand; Dormoy, Jean-Robert; Mach, Mateusz; Makosza, Mieczyslaw; Pankowski, Jacek
PATENT ASSIGNEE(S): Sanofi, Fr.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

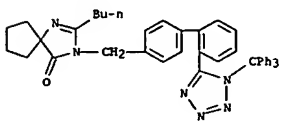
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906398	A1	19990211	WO 1998-FR1651	19980727
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2766821	A1	19990205	FR 1997-9653	19970729
AU 9888684	A1	19990222	AU 1998-88684	19980727
PRIORITY APPLN. INFO.:			FR 1997-9653 A	19970729
			WO 1998-FR1651 W	19980727

OTHER SOURCE(S): CASREACT 130:168359; MARPAT 130:168359

AB 4-R1C6H4C6H4(CH2R)-4 (R = phthalimido)[I; R1 = 4(4)-(di)methyl-2-oxazolin-2-yl] were prepared as synthetic intermediates. Thus, 2-PhC6H4CO2H was cyclocondensed with Me2CH(NH2)CH2OH and the product condensed with phthalimide and trioxane to give I (R1 = 4,4-dimethyl-2-oxazolin-2-yl). The latter was used in synthesis of irbesartan a cardiovascular agent.

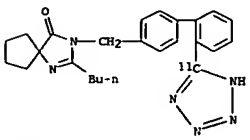
IT 138402-10-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)

RN 138402-10-5 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-[1-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



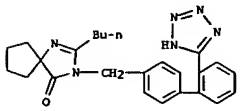
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:644226 CAPLUS
DOCUMENT NUMBER: 127:307342
TITLE: Radiosynthesis of [tetrazolyl-11C]irbesartan, a non-peptidic angiotensin II antagonist
AUTHOR(S): Ponchant, M.; Demphel, S.; Hinnen, F.; Crouzel, C.
CORPORATE SOURCE: DRM, Service Hospitalier Frederic-Joliot, Orsay, 91401, Fr.
SOURCE: European Journal of Medicinal Chemistry (1997), 32(9), 747-752
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB With the aim of visualizing myocardial angiotensin II receptors (AT1 subtypes), [tetrazolyl-11C]2-n-butyl-2-[(2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazoline-5-one ([tetrazolyl-11C]irbesartan) was synthesized in one pot in four steps from [11C]hydrogen cyanide. The labeling process which yielded [tetrazolyl-11C]irbesartan is described in detail and could be applied to the labeling of other ligands which possess the (1H-tetrazol-5-yl) moiety. Positron emission tomog. (PET) studies were performed in dogs. Heart, lung and blood time-activity curves did not change. Therefore this new radioligand is not suitable for studying myocardial angiotensin II receptors with PET.
IT 197440-08-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(radiosynthesis of [tetrazolyl-11C]irbesartan)
RN 197440-08-7 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl-5-11C)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

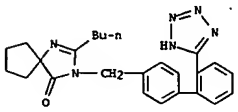


REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

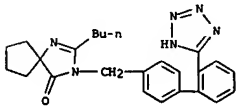
L5 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:519605 CAPLUS
DOCUMENT NUMBER: 127:185137
TITLE: Irbesartan. Antihypertensive, treatment of congestive heart failure, angiotensin II AT1 antagonist
AUTHOR(S): Casas, A.; Merlos, M.; Castaner, J.
CORPORATE SOURCE: Servei Nefrologia, Hospital Clinic Provincial Barcelona, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (1997), 22(5), 481-491
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 66 refs. in which the authors discuss the synthesis , pharmacol. actions, clin. studies, pharmacokinetics and metabolism of irbesartan. The use of this drug as an antihypertensive, an angiotensin II AT1 antagonist and in the treatment of congestive heart failure is also discussed.
IT 138402-11-6P, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(irbesartan synthesis, pharmacokinetics, metabolism and pharmacol. uses)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:671261 CAPLUS
DOCUMENT NUMBER: 121:271261
TITLE: Imidazolinones as nonpeptide angiotensin II receptor antagonists
AUTHOR(S): Quan, Mimi L.; DeLucca, Inda; Boswell, George A.; Chiu, Andrew T.; Wong, Pancras C.; Wexler, Ruth R.; Timmermans, Pieter B. M. W. M.
CORPORATE SOURCE: Dupont Merck Pharm. Co., Wilmington, DE, 19880-0402, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(12), 1527-30
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of biphenyl imidazolinones were synthesized as nonpeptide angiotensin II receptor antagonists. While those compds. with a tetrazole functionality were AT1 selective, those with a sulfonamide moiety showed affinities for both the AT1 and the AT2 sites. Representative compds. were very active in lowering blood pressure in conscious renal hypertensive rats following i.v. administration.
IT 138402-11-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(imidazolinones as nonpeptide angiotensin II receptor antagonists with antihypertensive activity)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:235405 CAPLUS
DOCUMENT NUMBER: 120:235405
TITLE: Development of tetrazole bioisosteres in angiotensin II antagonists
AUTHOR(S): Ferrari, B.; Taillades, J.; Perreaut, P.; Bernhart, C.; Gougat, J.; Guiraudou, P.; Cazaubon, C.; Roccon, A.; Nisato, D.; et al.
CORPORATE SOURCE: Sanofi Rech., Monpellier, 34184, Fr.
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(1), 45-50
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The application of acidic heterocycles as a substitute for tetrazole in the synthesis of potent non-peptide angiotensin II AT1 receptor antagonists is described.
IT 138402-11-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and angiotensin II antagonist activity of)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



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         10788 TRITYL?
L6           4 L5 AND TRITYL?

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L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:696369 CAPLUS
DOCUMENT NUMBER: 141:225515
TITLE: Synthesis of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-zion
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072064	A1	20040826	WO 2004-US3604	20040205
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004242894	A1	20041202	US 2004-773414	20040205
PRIORITY APPLN. INFO.:			US 2003-445218P P	20030205
			US 2003-465905P P	20030428
OTHER SOURCE(S):			CASREACT 141:225515	

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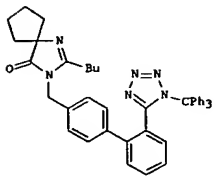


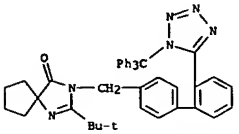
I

AB Provided are 5 methods of making 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-ene-4-one (I), e.g. comprising the steps of: (a) reacting 1-(N'-pentanoylamino)cyclopentanecarboxylic acid amide with 5-(4'-

L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole in the presence of an inorg. base, a solvent and a phase transfer catalyst; (b) cooling the mixt.; (c) adding water to the mixt. whereby two phases are obtained; (d) sepg. the two phases obtained; and (e) recovering the compd. I. The compds. I can be converted to irbesartan which is a known angiotensin II receptor antagonist (blocker).

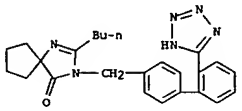
IT 745814-09-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

RN 745814-09-9 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-(1,1-dimethylethyl)-3-[[2'-[1-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



IT 138402-11-6P, Irbesartan
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(methods for preparation of 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4,4]-non-ene-4-one)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:633925 CAPLUS
DOCUMENT NUMBER: 141:157121
TITLE: Synthesis of irbesartan
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-zion
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004065383	A2	20040805	WO 2004-US1135	20040116
WO 2004065383	A3	20041216		
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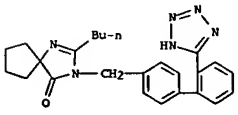
US 2004192713	A1	20040930	US 2004-759906	20040116
EP 1509517	A2	20050302	EP 2004-702955	20040116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2003-440997P P	20030116
			WO 2004-US1135 W	20040116
OTHER SOURCE(S):			CASREACT 141:157121	

AB Provided are a method of making irbesartan via a Suzuki coupling reaction and a novel intermediate, 2-butyl-3-(4'-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one, for such process. The novel process includes the step of reacting such intermediate with a protected tetrazolylphenylboronic acid.

IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(synthesis of irbesartan)

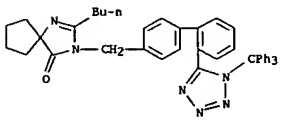
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



IT 138402-10-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of irbesartan)

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

RN 138402-10-5 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-[1-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

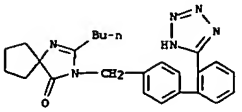


L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:60496 CAPLUS
DOCUMENT NUMBER: 140:111420
TITLE: Synthesis of irbesartan
INVENTOR(S): Nisnevich, Gennady; Rukhman, Igor; Pertsikov, Boris; Kaftanov, Julia; Dolitzky, Ben-Zion; Shapiro, Eugeny; Yahalomi, Bonit
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

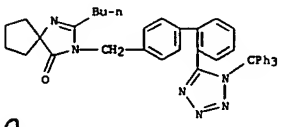
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004007482	A2	20040122	WO 2003-US22479	20030716
WO 2004007482	A3	20040527		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2492779	AA	20040122	CA 2003-2492779	20030716
EP 1546135	A2	20050629	EP 2003-764805	20030716
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005176794	A1	20050811	US 2003-621623	20030716
PRIORITY APPLN. INFO.:			US 2002-396424P P	20020716
			US 2002-402490P P	20020809
			WO 2003-US22479 W	20030716

OTHER SOURCE(S): CASREACT 140:111420
AB Irbesartan is prepared by reaction of 2-butyl-1,3-diaza-spiro[4.4]non-1-ene (I) with 5-(4-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole (II) in the presence of a phase transfer catalyst. Thus, reaction of I with II in toluene in the presence of Bu4NHSO4 at 90° for 1.5 h gave, after deprotection, 84.3% irbesartan. Also provided is irbesartan having a fine particle size.
IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of irbesartan)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



IT 138402-10-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of irbesartan)
RN 138402-10-5 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1-(triphenylmethyl)-1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



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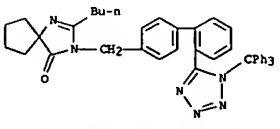
L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:113674 CAPLUS
DOCUMENT NUMBER: 130:168359
TITLE: Preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls
INVENTOR(S): Castro, Bertrand; Dormoy, Jean-Robert; Mach, Mateusz; Makosza, Mieczyslaw; Pankowski, Jacek
PATENT ASSIGNEE(S): Sanofi, Fr.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

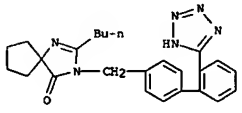
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906398	A1	19990211	WO 1998-FR1651	19980727
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2766821	A1	19990205	FR 1997-9653	19970729
AU 9888684	A1	19990222	AU 1998-88684	19980727
PRIORITY APPLN. INFO.:			FR 1997-9653 A	19970729
			WO 1998-FR1651 W	19980727

OTHER SOURCE(S): CASREACT 130:168359; MARPAT 130:168359
AB 4-R1C6H4C6H4(CH2R)-4 (R = phthalimido)[I; R1 = 4(4)-(di)methyl-2-oxazolin-2-yl] were prepared as synthetic intermediates. Thus, 2-PhC6H4CO2H was cyclocondensed with Me2CH(NH2)CH2OH and the product condensed with phthalimide and trioxane to give I (R1 = 4,4-dimethyl-2-oxazolin-2-yl). The latter was used in synthesis of irbesartan a cardiovascular agent.
IT 138402-10-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)
RN 138402-10-5 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-[1-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



IT 138402-11-6P, Irbesartan
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 2-oxazolinyl-4'-phthalimidomethylbiphenyls)
RN 138402-11-6 CAPLUS

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT